Biomedical Science

Regulation of Immunity by Anti-T-Cell Antibodies

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Antilymphocyte antibodies, in the form of antilymphocyte or antithymocyte sera, have long been used as immunosuppressive agents, particularly in the setting of organ transplantation. While effective, these antisera are far from ideal. They do not focus therapy on selected molecules or functionally distinct cell subsets, but rather react with a broad range of lymphocyte surface antigens. In addition, conventional antisera typically elicit a host immune response that can interfere with efficacy and that may cause toxicity. For years, these obstacles have substantially limited the value of antilymphocyte antibodies as therapeutic agents.

In recent years, the development of monoclonal antibodies (mAb) has rekindled interest in the therapeutic applications of antilymphocyte antibodies. It is now possible to produce homogeneous antibody preparations that can identify and selectively target distinct cell subsets, surface molecules, and secreted products that regulate immune function. This achievement has led to the development of several new strategies that are designed to suppress pathologic immune responses. Because of the pivotal role of T cells in the generation of immune responses, many of these strategies are focused on T-cell antigens.

Antibodies to CD3

Monoclonal anti-T-cell antibodies were first used successfully in humans to suppress renal allograft rejection. In prospective multicenter trials, a short course of mAb to the pan-T-cell antigen, CD3 (formerly designated T3), proved to be more effective than the use of high-dose corticosteroids and azathioprine in reversing the initial rejection crisis and promoting long-term graft survival in recipients of cadaveric renal allografts.[1] These early trials showed the feasibility of using anti-T-cell mAb to modulate immune function in humans, but they were complicated by several important problems that remain to be solved. First, the initiation of therapy with anti-CD3 mAb is accompanied by marked, albeit transient, systemic side effects, including fever, dyspnea, nausea, hypotension, and occasionally shock.[1] These effects may reflect the ability of anti-CD3 to activate T cells, causing the release of cytokines.[2] It may be possible to circumvent this problem by using anti-T-cell monoclonal antibodies that do not induce T-cell activation. Second, treatment with anti-CD3 mAb, like conventional antiserum, elicits an immune response in humans that precludes repeating therapy for recurrent rejection episodes.[1,3] Finally, anti-CD3 interferes with the function of all T cells, instead of focusing its effect on T-cell subsets that may be preferentially involved in recognizing and rejecting a graft. As I will describe, several alternative strategies are now being investigated in an effort to solve these problems. These strategies involve the use of monoclonal antibodies that are aimed at subsets of T cells rather than the entire T-cell population.

Antibodies to CD4

Many T-cell antigens have been considered as potential targets for immunosuppressive therapy with monoclonal antibodies (Figure 1). These include the CD4 and CD8 antigens that define the major T-cell subsets, as well as other antigens that are limited in their expression to activated T cells or to distinct families of T-cell antigen receptors. Among these, anti-CD4 mAb recently became the first to be subjected to clinical trials in humans.[4-7] These trials are based on mounting evidence from studies in animals showing that anti-CD4 mAb can suppress diverse autoimmune diseases[8-16] and can substantially prolong the survival of histoincompatible grafts.[17,18]

The most extensive examination of the effects of anti-CD4 mAb has been conducted in the NZB/NZW F_1 (B/W) mice model for systemic lupus erythematosus. An autoimmune disease spontaneously develops in these mice that closely resembles systemic lupus erythematosus in humans.[19] Female mice are more severely afflicted than male mice. They spontaneously produce numerous autoantibodies, including antibodies to double-stranded DNA, and they die young of immune-complex glomerulonephritis. Murine lupus in B/W mice can be prevented by the long-term administration of anti-CD4 mAb.[8] Moreover, even when treatment is delayed until severe lupus nephritis has developed, long-term therapy with anti-CD4 can reverse the clinical manifestations of systemic lupus and dramatically prolong life (Figure 2).[9]

The beneficial effects of anti-CD4 mAb are not limited to B/W mice. In two other murine models for systemic lupus erythematosus that are genetically unrelated to B/W mice, MRL/Mp-lpr/lpr and BXSB, the long-term administration of anti-CD4 retards autoimmunity.[10,11] Similarly, treatment with anti-CD4 suppresses the spontaneous development of autoimmune diabetes in nonobese diabetic mice.[12,13] Anti-CD4 is also effective in several experimentally induced murine autoimmune diseases.[14-16] These include experimental allergic encephalomyelitis,[14] a model for multiple sclerosis; collagen-induced arthritis,[15] a model for rheumatoid arthritis; and experimentally induced myasthenia gravis.[16] In experimental allergic encephalomyelitis, for example, a demyelinating disease of the central nervous system is induced by immunization with a spinal cord homogenate containing myelin basic protein (MBP). In control mice, immunization with MBP causes an autoimmune disease characterized clinically by rapidly progressive paralysis within two to

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ABBREVIATIONS USED IN TEXT

IL-2 = interleukin 2
mAb = monoclonal antibodies
MHA II = class II major histocompatibility antigen
MBP = myelin basic protein

three weeks. When the mice are treated with anti-CD4 during the early stages of neurologic deterioration, however, neurologic deficits can be reversed and progressive paralysis and death can be prevented.[14]

Based on the encouraging results of anti-CD4 therapy in murine models for autoimmunity, preliminary trials have been initiated in humans with autoimmune diseases.[4-7] Hafler and co-workers gave a short course of murine anti-CD4 mAb to four patients with chronic progressive multiple sclerosis.[7] This feasibility study did not examine therapeutic efficacy, but it showed that infusions of anti-CD4 were well tolerated clinically and did not produce the acute toxic effects seen previously in patients treated with anti-CD3.[1] Although this study was not designed to assess the suppression of disease activity, the suppression of immune function was documented by in vitro measurement of mitogen-induced stimulation of immunoglobulin synthesis. Disappointingly, despite this evidence of immune suppression, an immune response to the administered mouse mAb developed in three of the four subjects. In similar studies, Herzog and associates treated seven patients with rheumatoid arthritis with daily infusions of murine anti-CD4 mAb for a week.[4-6] Clinical side effects were minimal or absent. Immune suppression was demonstrated by a reversible inhibition of delayed-type hypersensitivity and by reduced in vitro T-cell proliferation, but, in this study, too, host immunity to the administered mAb developed in most of the patients. All patients reported a reduction in disease activity, but there were no untreated control subjects against whom to judge clinical efficacy.

The therapeutic value of anti-CD4 mAb will ultimately depend largely on our ability to block host immunity to the mAb and to minimize the suppression of normal immune function. With regard to the host immune response to therapy, recent studies in mice have shown that the immune response to xenogeneic (rat) mAb to CD4 is dose-dependent: low doses elicit an immune response, but high doses do not.[20] Furthermore, a short course of high-dose therapy induces long-term tolerance to the subsequent administration of lower doses that would ordinarily elicit an immune response.[21,22] Thus, it is possible that the immune response to anti-CD4 mAb in humans can be prevented either by sustained therapy with high doses of the mAb or by inducing tolerance initially with anti-CD4. Alternate solutions will have to be sought for other monoclonal antibodies that do not block the immune response to themselves. In certain circumstances, "humanized" antibodies composed of mouse variable regions inserted into human immunoglobulin molecules have been administered to people without eliciting a host immune response.[23] Concurrent conventional immunosuppressive therapy may also be helpful, although this has not prevented the development of host immunity to anti-CD3 mAb in transplant patients.[1]

Unfortunately, the requirement for high doses of anti-CD4 to block the host immune response to therapy has adverse implications for normal immune function. High-dose therapy profoundly depletes CD4+ cells in animals, abrogates humoral immune responses, and diminishes cellular immune responses.[20,21,24-27] Although CD4+ cells gradually reappear when treatment is stopped, a substan-

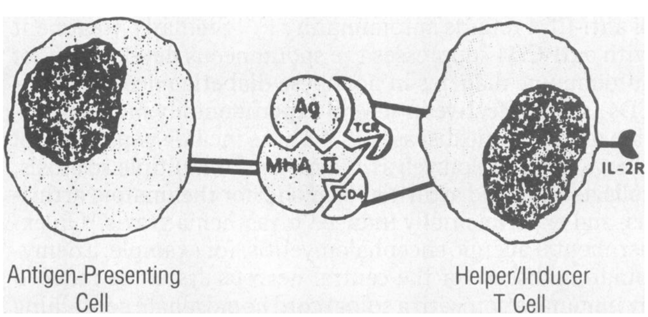

Figure 1.—Helper T cells recognize processed antigen (Ag) in association with class II major histocompatibility antigens (MHA II) on antigen-presenting cells. This recognition involves a T-cell receptor (TCR) that recognizes the Ag/MHA II complex. The interaction between T cells and antigen-presenting cells is facilitated by another T-cell surface molecule, CD4, that binds to MHA II. On exposure to Ag, activated T cells express additional surface molecules, such as the interleukin-2 receptor (IL-2R), that are not present on resting T cells. Based on this model, CD4, TCR, IL-2R, and MHA II may all be considered potential targets for immunosuppressive therapy.

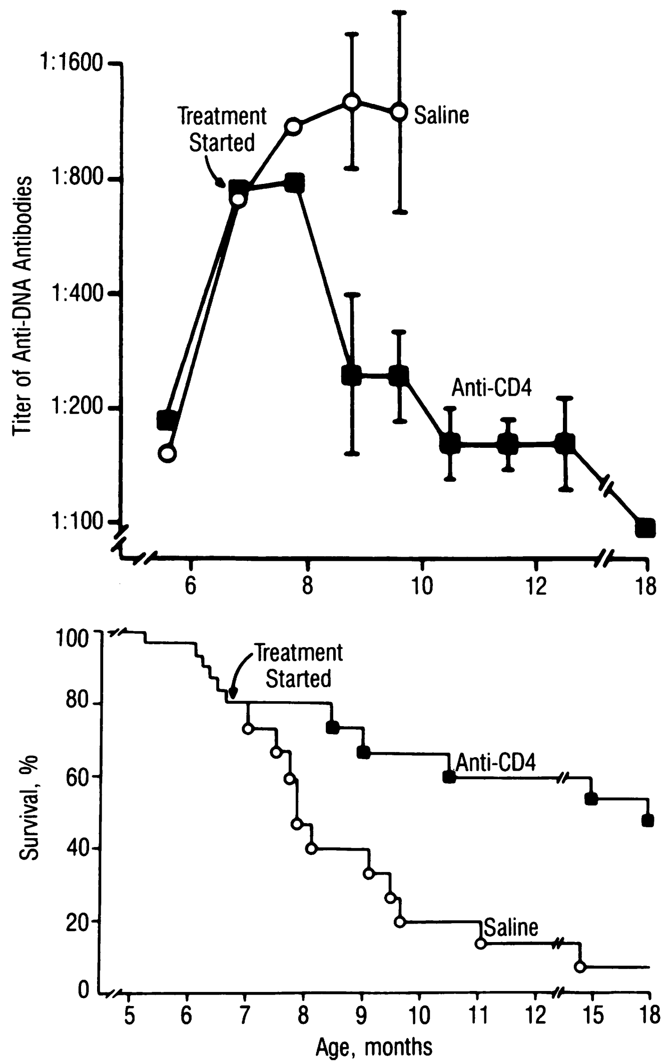

Figure 2.—Treatment with anti-CD4 retards murine lupus. Lupus-prone female NZB/NZW F_1 (B/W) mice received weekly injections of anti-CD4 (■) or saline (o) beginning at age 7 months. The top graph shows the geometric mean titer of antibodies to double-stranded DNA; the bottom indicates survival. The mice had advanced disease when treatment was initiated, as manifested by high titers of anti-DNA antibodies **(top)** and a 20% mortality rate in the original cohort **(bottom)** before therapy. Adapted from Wofsy and Seaman,[9] by copyright permission of the American Association of Immunologists.

tial depletion of target cells and the suppression of normal immune function persist for a prolonged period after the cessation of therapy.[26,27] These adverse effects can be minimized by the use of $F(ab')_2$ fragments of the mAb. The $F(ab')_2$ fragments bind CD4, inhibit target cell function, and thereby suppress autoimmunity.[22] Because the fragments lack the Fc portion of the molecule that is required for the clearance of antibody-coated cells, however, target cells are not depleted.[20,22] Consequently, the effects of the $F(ab')_2$ fragments on normal immunity are immediately reversible with the cessation of therapy (D.W., unpublished data, June 1989).

Antibodies to Activation Antigens

While it may be possible to minimize the toxicity of anti-CD4 mAb relative to high-dose corticosteroids and cytotoxic drugs, it would be far preferable to develop creative strategies to focus therapy more narrowly on the T cells that promote autoimmunity. One such strategy involves the use of mAb to antigens that are expressed on activated T cells. When T cells are activated, they express certain antigens that are not expressed on resting T cells. These activation antigens, which include the receptor for interleukin 2 (IL-2; see Figure 1), could serve as targets for specific therapy designed to interrupt active immune responses while sparing resting T cells. This hypothesis is supported by recent studies showing that mAb to the IL-2 receptor can be used in animals to suppress lupus nephritis and autoimmune diabetes.[28] Monoclonal antibodies to the IL-2 receptor have not yet been used to suppress immunity in humans, but they have been used with some success to treat humans with malignant T-cell tumors.[29] If these mAb continue to be well tolerated as chemotherapeutic agents, it is likely that they will soon be tested as immunosuppressive agents.

Antibodies to Antigen-Specific T-Cell Receptors

Ideally, therapy with anti-T-cell mAb would be directed against receptors that are expressed only by T cells that react with graft antigens (in transplant recipients) or autoantigens (in patients with autoimmune diseases). This strategy is based on the hope that alloreactive or autoreactive T cells might use a limited repertoire of T-cell receptor genes that is biased toward recognizing the disease-inducing antigens. Recent studies indicate that, at least in experimental allergic encephalomyelitis, such limited heterogeneity exists among antigen receptors on autoreactive T cells.[30] Specifically, MBP-reactive T cells use a limited subset of T-cell receptor genes; mAb directed against the products of these genes can be used to eliminate a pathologic portion of the T-cell receptor repertoire and thereby ameliorate autoimmune disease. It remains to be determined whether similar T-cell receptor targets can be identified in other clinical situations.

Antibodies to Major Histocompatibility Antigens

Many autoimmune diseases in humans are associated with particular HLA-DR antigens. These antigens, also referred to as class II major histocompatibility antigens (MHA II), play an important role in promoting immune responses. As suggested by Figure 1, the interaction between antigen-presenting cells and helper T cells can be blocked not only by mAb directed against the T-cell receptor or CD4 antigen on T cells, but also by mAb directed against MHA II on antigen-presenting cells. This suggests an appealing alternative to the use of anti-T-cell mAb to suppress autoimmunity: that is, it might be possible to retard autoimmunity by selectively interfering with the function of disease-associated MHA II. This possibility has generated great excitement recently because of the rapid progress that has been made in establishing the structure of MHA II molecules and identifying the precise sites on certain MHA II molecules that account for the predisposition to autoimmunity.[31] The enthusiasm for this approach is supported by the observation that mAb to MHA II can suppress autoimmunity in murine models for several human autoimmune diseases.[31-34] Because different MHA II molecules are co-expressed on the surface of antigen-presenting cells, the inhibition of selected MHA II might block pathologic immune responses associated with these molecules while sparing normal immune responses that can be mediated by other MHA II molecules. This might be achieved either with mAb to selected MHA II or with other agents designed to bind, and inhibit, disease-associated epitopes on MHA II molecules.

Summary

Current pharmacologic approaches to immune suppression leave much to be desired. The prevention of allograft rejection and the suppression of autoimmunity generally require treatment with corticosteroids or cytotoxic drugs, or both, which may not be sufficiently effective and which frequently cause serious immediate and long-term complications. With the advent of monoclonal antibody technology, it has become possible to identify and selectively inhibit distinct elements in the immune system that contribute to pathologic immune responses. This achievement has led to new therapeutic strategies that may be safer and more effective than the immunosuppressive therapies currently available. Many of these strategies focus on subsets of T cells because of the critical importance of T cells in immune responses. Monoclonal antibodies directed against CD4+ T cells, T-cell activation antigens, and T-cell receptor families have all shown promise in animal models and, in some cases, in preliminary human trials. The challenge now is to translate this promise into practical new forms of immunosuppressive therapy.

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